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I, KIM MARSHALL, MANAGER EXAMINATION SUPPORT AND SALES, hereby certify that the annexed is a true copy of the Provisional specification in connection with Application No. PP 4731 for a patent by PEPTECH LIMITED filed on 20 July 1998.

WITNESS my hand this Sixth
day of August 1999

KIM MARSHALL
MANAGER EXAMINATION SUPPORT AND SALES

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AUSTRALIA

Patents Act 1990

PEPTECH LIMITED

PROVISIONAL SPECIFICATION

Invention Title:

Bioimplant formulation II

The invention is described in the following statement:

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Field of the Invention:

The present invention relates to pharmaceutical and/or veterinary formulations for the sustained release of at least one active agent. In addition to the active agent(s), the formulations comprise stearin as an excipient and an agent which appears to form pores and/or cracks in the excipient to enable the release of the active agent(s).

Background of the Invention:

For reasons including improved efficacy of action and reduced frequency of administration, there is considerable interest in the development of pharmaceutical and veterinary formulations capable of controllably releasing an active agent for sustained periods (e.g. up to 6 months or more). Types of pharmaceutical agents that would particularly benefit from the development of such formulations are those which are typically administered by patients themselves over long periods (e.g. insulin). Formulations which achieve sustained release of such agents would improve patient compliance. In the veterinary context, sustained release formulations would reduce the stress often caused to the animal and veterinarian/owner alike by the need for repeated administration of an active agent.

The present applicant's have found that sustained release of an active agent in humans and other animals for periods of 7 days up to about 2 years, can be achieved by using a solid formulation comprising stearin as an excipient in combination with a substance which, while not wishing to be bound by theory, appears to form pores and/or cracks in the excipient to enable the release of the active agent.

Disclosure of the Invention:

Thus, in a first aspect, the present invention provides a pharmaceutical and/or veterinary formulation comprising about 2-15% (w/w) (on an active basis) of at least one active agent, about 0.5-10.0% (w/w) of a pore-forming agent and the balance stearin.

In a preferred embodiment of the present invention, the formulation comprises about 5-10% (w/w) (on an active basis) of at least one active agent, about 2.0-5.0% (w/w) of a pore-forming agent and about 85-93% (w/w) stearin.

With the proviso that the at least one active agent is not a GnRH peptide agonist or analogue, the at least one active agent may be selected from agents having pharmaceutical or veterinary significance and may be any or a combination of, for example, alkaloids (e.g. pilocarpine), catecholamines (e.g. dopa and epinephrine), sympathomimetic amines (e.g. ephedrine), hydantoins (e.g. phenytoin), prostaglandins, antiarrhythmic agents (e.g. quinidine), antibiotics, anti-protozoal agents (e.g. chloroquine), corticosteroids, fatty acids, peptides (e.g. hormones and antigens), polypeptides and proteins (e.g. hormones, antigens, antibodies, antibody fragments, receptors, transcription factors and enzymes), and nucleic acid compounds and derivatives such as DNA or RNA. The at least one active agent may have a molecular weight in the range of about 100 to about 100,000 or more. However, preferably, the at least one active agent has a molecular weight in the range of about 100 to about 50,000, more preferably, about 150 to about 5,000. Most preferably, the at least one active agent has a molecular weight in the range of about 1,000 to about 2,000.

Preferred active agents include:

(1) Somatostatin analogues

Particularly preferred somatostatin analogues include somatostin-14, octreotide, lanreotide and angiopeptin cyclopeptides (US 5569647).

Formulations according to the invention which include a somatostatin analogue as the at least one active agent may be used for treating, for example, hyperinsulinaemia and peptic ulcer.

(2) Lipid lowering agents

Particularly preferred lipid lowering agents include compounds which inhibit HMG CoA reductase such as simvastatin, pravastatin, mevastatin and lovastatin.

Formulations according to the invention which includes these agents may be used for treating, for example, hyperlipoproteineamias.

(3) Cyclosporins

Preferred cyclosporins include naturally occurring cyclosporins (e.g. as described by Dreyfuss *et. al.*, (1976) Europ. J. Appl. Microbiol. Vol. 3: 125-133), and analogues (e.g. as described by Wenger R.M. (1982), Chemistry of Cyclosporin A in "Cyclosporin "A", White D.G.G. ed., Amsterdam; Elsevier).

Formulations according to the invention which include a cyclosporin or cyclosporin analogue as the at least one agent may be used, for example,

as immunosuppressive agents for prophylaxis and treatment of organ rejection in allogeneic transplants.

(4) Acetylcholinesterase inhibitors

Preferred ACE inhibitors include angiotensin, captopril, enalapril and lisinapril.

Formulations according to the invention which include such agents may be used, for example, as antihypertensives.

(5) Calcitonins

Preferred calcitonins include human, salmon, and porcine calcitonin. Analogues of these polypeptides may also be suitable.

Formulations according to the invention which include calcitonin or calcitonin analogues may be used for treatment of, for example, hypercalcemia and for decreasing concentrations of phosphate in patients suffering from hyperparathyroidism, vitamin D intoxication, and osteolytic bone metastases.

The pore-forming agent may be any agent or combination of agents which enables the sustained release of the active agent from the stearin excipient. Preferably, the pore-forming agent or agents is/are selected from water-soluble agents such as inorganic salts (e.g. chlorides, phosphates and sulphates), organic salts (e.g. acetates, formates, propionates, glutamates, and aspartates), sugars (e.g. glucose, trehalose, mannose, galactose, sucrose and low molecular weight carbohydrates such as hydroxy propyl methylcellulose (HPMC) and carboxy methylcellulose (CMC), phosphatidylcholines (e.g. lecithin), aminosugars (e.g. glucosamine and galactosamine), amino acids/peptides (e.g. arginine, lysine, glutamic acid, aspartic acid, carnosine and aspartame), water-soluble proteins and water-soluble vitamins (e.g. Vitamin B).

Presently, the most preferred pore-forming agent is lecithin. Lecithin is a mixture of diglycerides of stearic, palmitic and oleic acids linked to the choline ester of phosporic acid.

The stearin excipient is preferably in a non-crystalline form. Stearin is partially hydrogenated palm oil having, as the principle fatty acids, C16:0(45%) and C18:0(53%). The melting point of stearin is about 60°C. It is believed that the use of stearin as the excipient contributes to the success of the formulations according to the invention, because it appears, surprisingly, to produce only a minimal to mild inflammatory response in a recipient

resulting in the encapsulation of the formulation within a thin layer of fibroblasts. It will be appreciated by persons skilled in the art, that alternative formulations comprising excipient(s) with similar characteristics to those included in the formulation defined above in the first aspect may likewise provoke minimal to mild inflammatory responses and consequently be useful for the sustained-release of an active agent. Such alternative formulations are to be regarded as falling within the scope of the present invention.

The formulations according to the invention may be for administration to humans and other animals selected from dogs, cats, other domestic animals, and captive wildlife.

Typically, the formulations will release the active agent, *in vitro*, into phosphate buffered saline (PBS: pH 7.3, prepared by dissolving 8.00 g of sodium chloride, 1.00 g di-sodium hydrogen phosphate anhydrous, 0.40 g sodium dihydrogen phosphate dihydrate (0.31 g if anydrous), and 0.05g sodium azide in 1 litre of deionised water), at 37°C at a rate of about 2-350 μg/day for at least 7 days and up to about 2 years. Further, the formulations will typically exist in the form of rods which have been extruded. In particular, extruded rods may be cut into predetermined lengths for implantation, by standard techniques, in the human or other animal. As will be readily appreciated, the length of rod will determine the rate and dose of the active agent. As opposed to implanting longer rods more than one rod can be implanted in each human or other animal.

In a second aspect, the present invention provides a method of treating a disease or condition in a human or other animal, the method comprising administering to the human or other animal the formulation of the first aspect of the invention.

Formulations for administration as implants, particularly to dogs, may be produced as follows:

Stearin (supplied as free flowing beads of 1mm or less in diameter made by Vandenberg Foods) and pore-forming agent are hand mixed using a spatula in a small beaker. The active agent may then be added and thoroughly mixed into the excipient and pore-forming agent mixture. The mixture can then be transferred to the barrel of a ram extruder that has a 1mm nozzle attached and is equilibrated to 55°C (or other temperature sufficient to soften the stearin). After attaching the ram, pressure (40 psi) is

applied until the product begins to extrude. At this point the pressure can be backed off and the product allowed to reach 55°C (or other temperature sufficient to soften the stearin). The product may then be extruded - 3g over a 30 second period. The resulting extrudate is then allowed to cool and then broken up and re-extruded through a 1mm nozzle to ensure uniformity of content throughout the mix. The 1mm nozzle may then be replaced with a 2.3mm diameter nozzle and the product extruded (using the same temperature equilibration procedure prior to extrusion). After cooling the long rods produced can be sectioned into lengths of the required weight and the sectioned lengths sterilised by gamma-irradiation.

Alternatively, formulation for administration as bioimplants may be produced by:

Stearin and pore-forming agent are mixed. The active agent may then be added and thoroughly mixed into the excipient and pore-forming agent mixture. The mixture can then be transferred to the barrel of an extruder that has a 1 mm nozzle attached and is equilibrated to temperatures sufficient to soften the stearin. The product may then be extruded. The resulting extrudate is then allowed to cool and then broken up and re-extruded through a 1 mm nozzle into a 2.3 mm mould which has been previously warmed to approximately 50°C to allow the mould to fill. The rods are removed from the mould and may be terminally sterilised.

The term "on an active basis" is to be given its usual meaning in the art. That is, it is used to indicate that the % amount (w/w) of peptide agonist or analogue present in a formulation is based on the dry weight of the peptide agonist or analogue.

The terms "comprise", "comprises" and "comprising" as used throughout the specification are intended to refer to the inclusion of a stated step, component or feature or group of steps, components or features with or without the inclusion of a further step, component or feature or group of steps, components or features.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Dated this 20th day of July 1998

PEPTECH LIMITED
Patent Attorneys for the Applicant:

F B RICE & CO